minor groove of the targeted RNA molecules. The presence of the compound within the minor groove inhibits RNA function.

The claims have been amended to more clearly recite what applicant considers to be his invention. Most of the amendments adopt suggestions made by the Examiner in the Office Action mailed August 29, 1995. Support for the amendment to claim 1 can be found at least in the preamble of claim 1 and in the first paragraph on page 5. Claim 1 has also been amended to recite a singular compound in order to establish proper antecedent basis for claim 9 and to more clearly recite what applicant considers to be his invention. Support for the amendment to claim 4 can be found at least in Example 6 (page 44) where inhibition of protein synthesis by inactivation of tRNA molecules by binding to a specifically targeted compound is discussed. Support for the amendment to claim 5 can be found at least in original claim 5. Support for the amendments to claim 7 can be found at least on page 9, lines 5-11 and Examples 1-3. Claim 9 was amended to establish proper antecedent basis from claim 1. Support for new claims 20 and 21 can be found at least in original claims 10 and 13, the fourth full paragraph on page 39 and in the first full paragraph on page 41. The retroviral subject matter of claims 10 and 13 has been deleted from those claims and incorporated into new claims 20 and 21.

In the Office Action mailed August 29, 1995, the Examiner stated that, since no declaration averring that the amendatory material consists of the same material incorporated by reference in the referencing application, the amendments to the specification were not entered. Applicant regrets this oversight. In this Amendment and Response to Office

Action, applicant has proposed the same amendments to the specification. Applicant notes that the amendment to page 37, line 29, recites the relevant portion of Ripka, the amendment to page 37, line 30, recites the relevant portion of McKinaly and Rossmann, the amendment to page 37, line 32, recites the relevant portion of Perry and Davies, the amendment to page 37, line 33, recites the relevant portion of Lewis and Dean, and the amendment to page 37, line 35, recites the relevant portion of Askew et al. The required Declaration by Patrea L. Pabst is submitted along with this Amendment and Response to Office Action.

Rejection Under 35 U.S.C. § 112, first paragraph

In the Office Action mailed August 29, 1995, the Examiner objected to the specification and rejected claims 1 and 3-19 under 35 U.S.C. §112, first paragraph, on the basis that the claims were not enabled by the specification. Applicant respectfully traverses this rejection.

The rejection analyzes the claims and disclosure as suggested in *Ex parte Forman*, 230 USPQ 546 (Bd. App. 1986). The rejection first states that the specification "does not distinctly describe procedures to perform any of the steps of the method." Applicant first notes that there is not requirement that applicant "distinctly describe procedures" to perform a claimed method. All that is required is that one skilled in the art be able to make or use the claimed invention based on the disclosure *coupled with information known in the art* without undue experimentation (see MPEP § 2164.01). The rejection appears to imply that the claimed invention requires a recitation in the specification of specific conditions for

performing the claimed process steps. Applicant asserts that there is no requirement that such specific description be provided so long as one of skill in the art could practice the invention using the disclosure combined with knowledge in the art. Applicant submits that the amount of description required depends upon the state of the art, the skill level in the art, and the nature of the invention. In the present case, applicant has provided in the specification myriad references to knowledge and procedures relevant to practicing the invention available at the time the invention was made. In addition, applicant has provided additional references published prior to the effective filing date of the present application (see from page 7, lines 7, to page 8, line 18, of the Response to Final Office Action mailed June 29, 1993) that described examples of procedures referred to in the specification as useful (see from page 6, line 24, to page 46, line 35). Applicant has also previously submitted a Declaration of Dr. Paul R. Schimmel Under 37 C.F.R. § 1.132 (mailed July 30, 1992), providing an expert opinion on the state of the art and the skill and knowledge level of those in the art at the time the invention was made and concluding that the steps in the claimed method could be routinely performed. Accordingly, applicant submits that the tools needed to perform the claimed method that are referred to in the specification were well known and could be used in the claimed method, as described in the specification, without the need for undue experimentation.

The rejection also asserts that there is little guidance in the specification for the steps of determining the secondary structure and three dimensional structure of an RNA molecule, synthesizing a compound that will bind specifically to the critical site, and demonstrating that

the synthesized compound can be used therapeutically . Applicant submits that the rejection has not presented convincing evidence or argument that specific conditions need to be recited in the specification to enable one of skill in the art to perform these steps. Thus, the rejection does not meet the burden of establishing a *prima facie* case of lack of enablement. Furthermore, applicant notes that the principles of all three of these steps are well established in the art and that those of skill in the art were aware of, and could routinely apply, known and established methods of structural analysis, mutagenic analysis, design of compounds to fit specific structures, and measure therapeutic effects of administered compounds.

The rejection also states that the examples fail to demonstrate all of the steps of the claimed method. This implies that applicant must provide a single example that embodies the entirety of a claimed method. Applicant first notes that there is no requirement that any examples be present in the specification. Applicant is also unaware of any requirement the entire claimed method be actually exemplified as a unit. This aspect of the rejection appears to assume that the circumstances of the state of the art and the nature of the invention require such an example. However, the rejection fails to make this argument and fails to provide any convincing evidence or argument to establish that such an example is required to allow those of skill in the art to practice the invention without undue experimentation. Applicant submits that the propriety and essential nature of any "requirements" asserted by the Examiner must be established by the Examiner in order to establish a *prima facie* case of lack of enablement.

The rejection also states that no guidance is given for the therapeutic use of a compound produced by the method of the invention. Applicant respectfully disagrees. The specification provides specific guidance for the administration of compounds of the invention from page 39, line 31, to page 41, line 29.

The rejection also questions whether that state of the art was sufficiently developed to allow routine design of compounds that interact with RNA as required by the claims. The rejection asserts that relatively little progress has been made towards generating compounds that specifically interact with critical sites on RNA molecules. However, the rejection fails to establish either the validity or the probative value of this assertion. For example, since the public is not aware of the method disclosed in the present application, it is not clear what the public's alleged failure to produce compounds that interact with the minor groove of RNA says about the enabling effect of this application. Applicant asserts that, because of this, because it is not clear how much effort has been exerted to produce compounds of the invention, and because it is not clearly established on the record that compounds of the invention cannot be produced without difficulty, this assertion carries little weight in establishing the level of enablement of the claims. In this regard, applicant notes that Wilson et al., *Biochemistry* 32:4098-4104 (1993), cited in the rejection, appears to describe *initial* efforts, apparently started years after the present invention was made, to identify compounds that interact specifically with RNA. In addition, Wilson et al. describes not efforts to synthesize such compounds, but a screening of compounds with known interactions with *DNA*. The probative value of the comment by Wilson et al. that no classes of small

molecules have been defined that bind strongly to the minor groove of RNA has not been established insofar as Wilson et al. does not characterize any attempts to do so. Similarly, the probative value of the comment by Wilson et al. that there are no outstanding paradigms to suggest design directions for RNA groove-binding drugs is in serious doubt because the present application, unknown to Wilson et al., describes such a paradigm. Furthermore, this belief expressed in Wilson et al. that no such paradigm exists indicates that Wilson et al. was unaware of any systematic effort to *design* compounds that interact with RNA molecules based on any paradigm such as the one conceived by applicant. Thus, the alleged failure to produce such compounds contained in Wilson et al. is not indicative of any difficultly in practice of the present invention.

Finally, the rejection repeats the erroneous assertions that there is no description in the specification of how to practice the invention and that the state of the art was such that no procedures existed for producing inhibitory compounds. Such assertions have (1) not been sufficiently established by convincing evidence or argument to establish a *prima facie* case of lack of enablement, and (2) applicant has pointed out where in the specification and in the prior art specific procedures and principles useful in the practice of the claimed invention can be found, thus establishing that the assertions contained in the rejection are in error. In addition, applicant has amended the specification to include the material incorporated by reference as previously required by the Examiner.

Applicant respectfully submits that, for all of the foregoing reasons, the present claims meet the standards of 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, second paragraph

In the Office Action mailed August 29, 1995, the Examiner maintained the rejection of Claims 1 and 3-19 under 35 U.S.C. § 112, second paragraph as being indefinite. Applicant respectfully traverses this rejection to the extent that it is applied to the claims as amended.

Applicant appreciates the Examiner's critical attention to the clarity of the claims. Responsive to the bases of this rejection, applicant has attempted to amend the claims as suggested by the Examiner and/or to more clearly recite what applicant considers to be his invention. Applicant believes that all of the grounds of rejection under 35 U.S.C. § 112, second paragraph are moot in view of the amendments.

Regarding the basis involving claims 1, 3, 6-10, and 14-16, claim 1 has been amended to include, as a result of the process steps, the result called for in the preamble of claim 1.

Regarding the basis involving claim 4, claim 4 has been amended to more clearly recite the relationship between inhibition of protein synthesis and inhibition of the targeted ribonucleic acid function.

Regarding the basis involving claims 4 and 5, applicant believes that claim 4 has been amended such that the recitation of protein synthesis does not require any antecedent basis in base claim 1. Claim 5 has been amended to depend from claim 4 such that the recitation of "protein synthesis" in claim 4 provides antecedent basis for its recitation in claim 5.

Regarding the basis involving claim 5, claim 5 has been amended as suggested to recite "bacterial cells" rather than "bacteria."

Regarding the basis involving claim 7, claim 7 has been amended to refer to comparison of the function of the mutant and original RNA and to recite the relationship between any altered function observed and the determination of critical sites.

Regarding the basis involving claims 9 and 10, claim 9 has been amended to recite only "compound" and claim 1 has been amended to recite a singular compound in order to provide proper antecedent basis for the recitation of "compound" in claim 9.

Regarding the basis involving claims 10 and 13, the element "retroviral vectors" has been deleted from claims 10 and 13 and new claims 20 and 21 have been added to encompass the subject matter intended to be covered by original claims 10 and 13.

Applicant gratefully acknowledges the withdrawal of the rejection under 35 U.S.C. § 103.

Allowance of claims 1, and 3-21 is respectfully solicited.

Respectfully submitted,

Patrea L. Pabst
Reg. No. 31,284

Date: December 29, 1995

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Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Amendment and Response to Office Action, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea L. Pabst

Date: December 29, 1995

Appendix

1. A method for designing a compound specifically inhibiting targeted ribonucleic acid function comprising the steps of:

(a) determining the nucleotide sequence in the targeted ribonucleic acid that is critical to function;

(b) determining the secondary structure of the region of the targeted ribonucleic acid in which the critical site is located;

(c) determining the three-dimensional structure of the targeted RNA, including the position of the critical site relative to the major and minor grooves;

(d) determining the sequence of nucleotides and structure flanking the critical site in the targeted ribonucleic acid that is specific to the critical region of the ribonucleic acid to be inhibited and within the minor groove; and

(e) synthesizing a compound that will bind specifically to the critical site within the minor groove of the targeted ribonucleic acid thereby inhibiting targeted ribonucleic acid function.

3. The method of claim 1 wherein the ribonucleic acid is selected from the group consisting of mRNA, rRNA, tRNA and viral RNA.

4. The method of claim 1 wherein inhibition of targeted ribonucleic acid function inhibits protein synthesis.

5. The method of claim 4 wherein protein synthesis is inhibited in cells selected from the group consisting of tumor cells, virally infected cells, and bacterial cells.

6. The method of claim 1 wherein the three-dimensional structure is modeled using sequences of the RNA and calculating the minimum energies for these structures.

7. The method of claim 1 wherein the critical region of the targeted ribonucleic acid is determined by mutation of regions of the targeted RNA and comparison of the function of the mutated RNA with the original RNA, wherein mutations that result in mutant RNA having altered function indicate that the site of mutation is a critical site.

8. The method of claim 1 wherein the targeted RNA is a tRNA, wherein the critical region of the tRNA is determined by site directed mutation of the tRNA and analysis of the function of the mutated tRNA.

9. The method of claim 1 further comprising determining an effective amount of the compound and combining the compound with a pharmaceutical carrier.

10. The method of claim 9 wherein the carrier is selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

11. A compound specifically binding to and inhibiting the function of a targeted RNA molecule, wherein the compound is specifically directed to and binds to a critical region of the RNA molecule, located within the minor groove of the RNA molecule, identified by a combination of the primary, secondary and tertiary structure of the critical region.

12. The compound of claim 11 wherein the RNA is selected from the group consisting of mRNA, tRNA, rRNA, and viral RNA.

13. The compound of claim 11 further comprising a pharmaceutically acceptable carrier selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

14. The method of claim 3 wherein the critical site is in the minor groove of the acceptor stem of a tRNA molecule.

15. The method of claim 14 wherein the tRNA molecule is $tRNA^{Ala}$.

16. The method of claim 15 wherein the critical site is the G3:U70 base pair.

17. The compound of claim 12 wherein the compound binds to a critical region within the minor groove of the acceptor stem of a tRNA molecule.

18. The compound of claim 17 wherein the tRNA molecule is $tRNA^{Ala}$.

19. The compound of claim 17 wherein the critical region is the G3:U70 base pair.

20. The method of claim 1 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.

21. The compound of claim 11 wherein the compound is a nucleic acid and the compound is synthesized *in vivo* from a retroviral vector.